

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No. PCT/GB2005/001241	International filing date (day/month/year) 30.03.2005	Priority date (day/month/year) 02.04.2004
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International Patent Classification (IPC) or both national classification and IPC
C07C233/43, C07C231/12, A61K31/167, A61P11/08

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material:
 in written format
 in computer readable form
 - c. time of filing/furnishing:
 contained in the international application as filed.
 filed together with the international application in computer readable form.
 furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application,
 claims Nos. 14 with respect to industrial applicability

because:

- the said international application, or the said claims Nos. 14 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for the whole application or for said claims Nos.
 the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

- has not been furnished

- does not comply with the standard

the computer readable form

- has not been furnished

- does not comply with the standard

- the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

- See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2005/001241

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-7
	No:	Claims	8-21
Industrial applicability (IA)	Yes:	Claims	1-13, 15-21
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/GB2005/001241

Item III.

Claim 14 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Item V.

- D1: WO 2004/011416 A - *Relevance phase II*
- D2: GOULD P L: "SALT SELECTION FOR BASIC DRUGS" INTERNATIONAL JOURNAL OF PHARMACEUTICS, AMSTERDAM, NL, vol. 33, no. 1/3, 1986, pages 201-217, XP002074725 ISSN: 0378-5173
- D3: WO 2004/106279 A - *Relevance crystalline Mono HCl*

1.) The opinion is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. Thus D3 is not considered to be relevant to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT. However, Applicant's attention is drawn to the fact that D3 might become relevant after entry in the regional phase. *- phase II*

D1 is considered to represent the closest prior art. D1 discloses (cf example 7b) a crystalline dihydrochloride salt and a crystalline hydrochloride salt having 1.52 equivalents of chlorine of N-(2-[4-((R)-2-hydroxy-2-phenylethylamino) phenyl] ethyl)-(R)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine and the use of the salt as beta-adrenergic receptor agonist. The salts are prepared by crystallisation from aqueous isopropanol/hydrochloric acid.

2.) The subject-matter of **claims 1-7** is novel in the sense of Article 33(2) PCT and involves an inventive step in the sense of Article 33(3) PCT over the disclosure of D1, since D1 does not disclose or suggest a process for preparing a monohydrochloride salt wherein a weak acid is used to effect selective protonation of II, followed by introducing chloride by anion exchange, followed by deprotection and isolation of the monohydrochloride.

The subject-matter of **claims 8-21** is novel in the sense of Article 33(2) PCT over the disclosure of D1, since D1 does not disclose crystalline (Ia) monohydrochloride with a DSC trace having no endothermic feature below 125°C/form II crystalline (Ia) monohydrochloride.

The subject-matter of claims 8-21 does not however involve an inventive step in the sense of Article 33(3) PCT. In the light of D1, the problem underlying claims 8-21 is the provision of a further form of N-(2-[4-((R)-2-hydroxy-2-phenylethylamino) phenyl] ethyl)-(R)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl) ethylamine which is suitable for pharmaceutical formulation, in particular for administration by inhalation.

It is considered that the skilled person, faced with the problem of providing such a suitable pharmaceutical form and starting from the dihydrochloride and the crystalline hydrochloride salt having 1.52 equivalents of chlorine of D1 would undoubtedly investigate the monohydrochloride salt. Furthermore D2 teaches that, when compared to monohydrochlorides, the dihydrochlorides may suffer from processing difficulties and D2 says that "the difference in the strength of the basic centres in dihydrochloride salts can lead to a gradual loss of one of the hydrochloride moieties by release of hydrogen chloride gas".

It is thus considered that the skilled person would have investigated the monohydrochloride salt of the compound in question, the properties of the monohydrochloride pseudopolymorph referred to claims 8-21 representing merely the results of standard tests which the skilled person would inevitably have carried out.

3.) For the assessment of the present claim 14 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VIII.

1.) In claim 1, the terms "weak acid" and "hydroxyl protecting group" are vague and blur

the scope of the claim, Article 6 PCT.

2.) In claim 8, the monochloride salt is only characterised by a DSC feature. In view of the fact that the description discloses only one example of such a salt (i.e. form 2) and that coming up with further salts having the DSC feature referred to cannot be achieved without undue burden, the relevant physical properties of the form 2 should be incorporated (X-ray data, IR data) in the claim, Article 6 PCT.

3.) In claims 12-18 the term "Form 2" lacks a generally accepted and known meaning and renders the claim unclear, Article 6 PCT.

4.) Although claims 8 and 12 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.